REMARKS

Claims 1, 5-14 and 28 presently appear in this case. No claims have been allowed. The official action of April 8, 2005, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for the treatment of inflammatory arthritis in a human subject by orally administering IB-MECA or Cl-IB-MECA in a daily amount of less than about 70 μg/kg.

The specification has now been reviewed and many typographical or clerical errors were noted that need correction. Accordingly, a substitute specification is attached as Appendix A, and a marked-up version of the specification as filed is attached as Appendix B. Pursuant to 37 CFR 1.125(b), the undersigned states that the substitute specification contains no new matter.

Claims 15-27 have been rejected under 35 U.S.C. §101 as being improper use claims.

Claims 15-27 have now been deleted, thus obviating this rejection.

Claims 1-3, 15, 16 and 28 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite with respect to "D_{MAX}."

The term objected to by the examiner no longer appears in any of the present claims. Accordingly, this rejection has now been obviated.

The examiner states that claims 15-27 are indefinite as it merely recites a use.

Claims 15-27 have now been deleted, thus obviating this rejection.

Claims 1-27 have been rejected under 35 U.S.C. §102(b) as being anticipated by Jacobsen. The examiner states that Jacobsen discloses compounds that are found to be selective A3 adenosine receptor agonists and related compositions and treatment methods. The examiner states that it includes use of IB-MECA or Cl-IB-MECA for the treatment of a disease state that may include inflammatory disorders, such as arthritis, and that the dosage will depend on a variety of factors and the size of the dose will be determined by the route, timing and frequency of administration, etc. The examiner states that suitable doses and dosage regimens can be determined by conventional range finding techniques known to those of ordinary skill in the art. The examiner states that the reference teaches that therapeutically effective dosages range from about 0.01 to about 10 mg/kg body weight per day and that there are a wide variety of suitable formulations, including formulations for oral, aerosol, parenteral,

subcutaneous, intravenous, intramuscular, interperitoneal, rectal and vaginal administration. This rejection is respectfully traversed.

The present invention is based on the unexpected discovery that when IB-MECA or Cl-IB-MECA are used for the treatment of inflammatory arthritis by means of oral administration, the active ingredient does not have a classic "dose response effect" wherein the higher the dosage the more pronounced the effect. Rather, it was unexpectedly and surprisingly found that an increase in the dosage caused a decrease in the therapeutic effect. See, for example, Example 1B; see also the present specification at pages 6 and 7, paragraphs [0013] - [0015]. Thus, the findings of the present invention pave the way to the development of a therapeutic regimen where effective treatment of arthritis can be achieved by administering low oral doses of IB-MECA or Cl-IB-MECA with significantly lower risk of undesired side effects.

The unexpected results shown in the present specification establish that any case of *prima facie* obviousness has been rebutted. However, the examiner has not made an obviousness rejection but only a 35 U.S.C. §102 rejection. Jacobsen has no examples within the scope of the present claims. However, Jacobsen lists a long list of indications (column 25, line 20, to column 26, line 19),

including indications as diverse as high blood pressure, depression, infertility, cardiac failure, acute head injury, kidney disease, and Alzheimer's disease. Among this long list of various and sundry indications is "inflammatory disorders, such as ... arthritis" (column 25, lines 39-40). Jacobsen also lists a long list of administrative methods, among which, as noted by the examiner, are oral, aerosol, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, rectal and vaginal administration. Jacobsen also has a long list of possible active agents that extends from column 5, line 65, to column 8, line 64. Among this long list of compounds is IB-MECA. Furthermore, Jacobsen ambiguously discloses a very large range for dosages that, if it encompasses the present dosages at all, the presently claimed dosages are only a very, very small part of the broad range of the reference.

With respect to the dosage range, Jacobsen discloses at column 27, lines 21-24:

> Exemplary dosages range from about 0.1 to about 100 mg/kg body weight of the animal being treated/day. Therapeutically effective dosages range from about 0.01 to about 10 mg/kg body weight/day.

The present claims are set forth in the units of μg/kg and require a dose of less than 70 μg/kg. When converting the units of Jacobsen to μg/kg, it can be seen that the exemplary

dosages range from about 100 to about 100,000 μg/kg. This is wholly outside of the range of the present claims. However, cryptically, the following sentence states that therapeutically effective dosages range from about 10 to about 10,000 μg/kg body weight/day. Thus, the minimum amount in the exemplary dosages is much higher than the minimum amount in the therapeutically effective dosages. While the minimum amount of the second recited range falls within the range of the present claims, only the very bottom part of that range, i.e., 10-70 μg/kg, fall within the present claims, and the vast majority of that range, 71-10,000 μg/kg is outside of the presently claimed range.

The examiner's attention is invited to MPEP §2131.03.II, with the heading:

> II. PRIOR ART WHICH TEACHES A RANGE WITHIN, OVERLAPPING, OR TOUCHING THE CLAIMED RANGE ANTICIPATES IF THE PRIOR ART RANGE DISCLOSES THE CLAIMED RANGE WITH "SUFFICIENT SPECIFICITY"

This section reads:

> When the prior art discloses a range which touches, overlaps or is within the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." What constitutes a "sufficient specificity" is fact dependent. If the claims are directed to a narrow

> range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range, depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. The unexpected results may also render the claims unobvious. The question of "sufficient specificity" is similar to that of "clearly envisaging" a species from a generic teaching. See MPEP §2131.02. A 35 U.S.C. 102/103 combination rejection is permitted if it is unclear if the reference teaches the range with "sufficient specificity." The examiner must, in this case, provide reasons for anticipation as well as a motivational statement regarding obviousness. *Ex parte Lee*, 31 USPQ2d 1105 (Bd. Pat. App. & Inter. 1993) (expanded Board). For a discussion of the obviousness of ranges see MPEP §2144.05. [Emphasis added]

It is urged that on the facts of this case, the claimed method, which requires a selection of two from many active compounds, one from many modes of administration, one from a large selection of indications, and a very, very small part of a very large range, is not a disclosure of "sufficient specificity" to constitute an anticipation of the claims. A selection must be made of IB-MECA or Cl-IB-MECA. Furthermore, the selection must be made of inflammatory arthritis from among the columns of indications in Jacobsen. One must select oral administration from the nine types of administration noted by the examiner in the rejection, and one must select less than 70 μg/kg from a range that extends all the way up to

100,000 μg/kg. With all of these selections, and with such a tiny part of the range being selected, it cannot be said that the present method is disclosed with "sufficient specificity" to constitute an anticipation of the claims.

Furthermore, as stated in the above-quoted portion of the MPEP, the evidence of unexpected results within the narrowed claim range is further evidence to make it reasonable to conclude that the narrow range is not disclosed with "sufficient specificity." It should be noted that the case of *Ex parte Lee* cited in the above-quoted portion of the MPEP indicates that the decision is fact based. In *Lee*, the case of *In re Arkley*, 172 USPQ 524 (CCPA 1972), was distinguished because "the facts in this case do not involve any 'need for picking, choosing and combining various disclosures not directly related to each other by the teachings of the cited reference.'" *Ex parte Lee*, *supra*, at 1107. Here, there is a substantial need for picking and choosing from the various disclosures in Jacobsen. One must pick and choose from the active ingredients; one must pick and choose from the methods of administration; and one must pick and choose from the indications; let alone picking and choosing within the cited dosage range in order to end up with the method of the present invention.

Accordingly, *Ex parte Lee* is not dispositive of this case for the reasons clearly explained in the MPEP. With the facts in this case, the examiner is fully justified in determining that the present method is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. Because of the unexpected results, the claims are also rendered unobvious. Accordingly, reconsideration and withdrawal of this rejection are earnestly solicited.

It is submitted that all of the claims now present in the case clearly define over the references of record. Reconsideration and allowance are, therefore, earnestly solicited.

Respectfully submitted,

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